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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Acti n Summary	Applicati n N .	Applicant(s)	
	09/506,942	BALLOUL ET AL.	
	Examiner	Art Unit	
	Shanon A. Foley	1648	

-- The MAILING DATE of this communication app ars n th c ver sheet with th corresp ndence address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,24 and 32-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23, 24, and 32-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing R view (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Applicant has cancelled previously pending claims 10-20 and 25-31 and added new claims 32-56. Claims 23 and 24 are also pending and were previously rejected in the previous Office action. These claims were inadvertently left off of the cover sheet. Therefore, claims 23, 24, and 32-56 are under consideration.

Priority

Applicant argues on pages 16-17 of amendment C that Stanley et al. in WO 96/29091 is not available under U.S.C. §102(a) because Stanley et al. was published September 26, 1996 and the claim to foreign priority in the instant application is French application number 96 09584 filed on July 30, 1996.

Although the Examiner has acknowledged the claim to foreign priority, applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. Therefore, the teachings of Stanley et al. in WO 96/29091 are available under U.S.C. §102(a) as prior art.

Claim Objections

Claims 23, 24, 44-46 and 48 are objected to because of the following informalities:

Claims 23 and 24 are objected to as being dependent upon a rejected base claim 10.

Applicant is advised that should claims 23 or 24 be found allowable, claims 53 or 54 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing,

despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 44, line 2 recites "...for At least...".

Claims 45, 46, and 48 recite "interleukine"

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is drawn to a recombinant vector encoding at least one early polypeptide and at least one late polypeptide from the papillomavirus, with the exception of a DNA sequence encoding E7 and L2. Subsequent dependent claims 39-41, 43, 53, and 54 state that the early polypeptides E6 and/**or** E7 and L1 and/**or** L2. Therefore, the composition of the dependent claims are contradictory to the independent claim and it is unclear what Applicant intends.

Applicant argues on pages 24-25, 27-28 and Exhibit A of amendment C, that exclusion of L2 and E7 from the claims is justified because of recent data reporting the inefficiency of these compositions.

Although recent evidence has developed pointing to a lack of enablement for some of the embodiments in the instant Application, an exclusion of specific elements (E7 and L2) were not

in the original claims or specification. Therefore, Applicant cannot add this exclusion to these particular embodiments.

Applicant states on page 15 of the amendment that "variant" is not recited in the new claims.

However, claims 39 and 41 are drawn to a native, chimeric, or variant of a papillomavirus polypeptide. How can a polypeptide still be considered "native" if it is taken out of the papillomavirus genome and inserted into a recombinant vector in claim 32? In addition, a "variant" of a polypeptide fails to adequately define the metes and bounds intended in terms of the homologous structural components or similar functionality of other substances that could define a "variant" of the papillomavirus polypeptides claimed.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The added material which is not supported by the original disclosure is as follows: claim 32 is now directed to at least one early polypeptide and one late polypeptide from the papillomavirus with the specific exception of E7 and L2 combination. This negative limitation cannot be found in the original disclosure.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claims 32, 39, and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a genus of chimeric and variant polypeptides from the papillomavirus. The specification does not teach structural elements these chimeric or variant polypeptides must possess to ensure proper function to practice the invention. Since the genus encompasses a variety of possible variants of each polypeptide, a single non-oncogenic species of E6 and E7 is not seen as representative for the full genus claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 23, 24, 32-34, 39-45, 52-56 are rejected under 35 U.S.C. 102(a) as being anticipated by Stanley et al. in WO 96/29091.

Applicants arguments have been considered, but are unpersuasive for the following reasons:

Applicant argues that Stanley et al. (WO 96/29091) is not properly available 35 U.S.C. 102(a) and found the US Patent equivalent in 6,096,869 and bases arguments on the newly cited patent to respond to arguments.

Reasons for why Stanley et al. is properly available under 35 U.S.C. 102(a) is discussed above under "priority". Therefore, responses to arguments presented by Applicant will be based on the originally cited WO 96/29091 by Stanley et al.

Applicant argues that Stanley et al. does not teach every element of the claimed invention because Stanley et al. teaches a composition that comprises (i) IL-12 and (ii) a papillomavirus antigen (noted on page 4, lines 29-32 of the WO reference). Applicant argues the teachings of Stanley et al. to mean that only one papillomavirus antigen is encoded and the antigen can comprise one or more of the listed proteins and therefore, the skilled artisan can interpret this as a fusion of many proteins (found on page 5, lines 5-8 of the WO reference). Applicant states that evidence of this teaching is confirmed by the experimental data where only one E7 or E6 protein is administered (found on page 19-20 of the WO reference). Applicant argues that this interpretation is further evidenced by the claim 5 (equivalent to claim 6 in the WO reference).

Applicant's interpretation of the teachings of Stanley et al. is not convincing when viewing the reference as a whole. Applicant's attention is directed to page 4, lines 33-37 and page 5, lines 2-8. The reference specifically states that (ii) can comprise at least one papillomavirus protein. The choice of proteins are selected from E1, E2, E4, E5, E6, E7, L1, and/or L2 (emphasis added). Therefore, the composition taught by Stanley et al. includes one, or more than one papillomavirus protein. On page 5, lines 2-5, page, Stanley et al. teaches that component (ii) can comprise a recombinant vector encoding at least one papillomavirus protein or fusion protein. On page 6, lines 5-8 and page 11, lines 21-25, the reference specifically teaches that the polynucleotide encoding IL-12 can be encoded by the same vector that encodes a

papillomavirus antigen, and can be encoded as separate proteins, or as fusion proteins. Therefore, the teachings of Stanley et al. are not limited to fusion proteins. Although Stanley et al. administers only E6 or E7 in the working example, the scope claims and the embodiments within the reference is not limited to the specific embodiments illustrated within the working example. Applicant is directed to the teachings of claims 4 and 5, which are drawn to a pharmaceutical composition that comprises a combination of IL-12 and at least one papillomavirus protein. Claim 6 recites "...at least one of the proteins E6, E7, L1, and/or L2..." (emphasis added). Applicant is also directed to subsequent claims 7, 8, 13-17.

Applicant argues that the teachings of Stanley et al. cannot be broadened to include to the use of a recombinant molecule encoding a non-IL-12 immunostimulatory molecule because IL-12 p40 is not expressed in normal tissues or non-regressing lesions, only regressing lesions express IL-12 p40.

Claims 1 and 3 of Stanley et al., for example, are drawn to using whole IL-12, not the specific subunit IL-12 p40. In addition, some of the claims in the instant application, such as claim 44, are open to including other materials, i.e., IL-12.

Applicant argues that the main conceptual difference in the teachings of the instant application and the teachings of Stanley et al. is that the presence of a IL-12 or any other cytokine is not compulsory in the instant application. Also, the invention involves special antigen combinations of polypeptides from the early and late regions. Applicant emphasizes that the instant invention involves expression of non-fused forms of the papillomavirus polypeptides.

It is evident that the instant application does not require the use of cytokines in all of the claims. However, the open claim language in the instant application uses "comprising", which

does not exclude the addition of other materials within the composition. Therefore, the teachings of Stanley et al., which include the use of IL-12 and "at least one papillomavirus protein selected from E6, E7, L1 and/or L2" anticipate the instant invention of comprising early and late polypeptides of the papillomavirus. Also, as discussed above on page 5, lines 2-5, page, Stanley et al. does not limit the proteins to be expressed in a fused form. The reference teaches that component (ii) can comprise a recombinant vector encoding at least one papillomavirus protein or fusion protein. Therefore, because the teachings of Stanley et al. include pharmaceutical composition comprising a vaccinia vector that encodes more than one papillomavirus protein that includes at least one early and one late, and an immunostimulatory molecule, in an unfused form, it is maintained that the teachings of Stanley et al. anticipate claims 23, 24, 32-34, 39-45, and 52-56.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35-38 and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al. in WO 96/29091 as applied to claims 23, 24, 32-34, 39-45, and 52-56 above, and further in view of Boursnell et al. (WO 92/16636), Meyer et al., Galloway, Hines et al., and Gajewski.

In response to the previous rejection, applicant argues that the previous rejection failed to demonstrate motivation or suggestion to combine, a reasonable expectation of success at the time

of the invention, and must teach each and every aspect of the claimed invention. Applicant further argues the references individually.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

As discussed previously, Stanley et al. teaches a pharmaceutical composition that comprises IL-12 and at least one papillomavirus protein. The choice of proteins is selected from E1, E2, E4, E5, E6, E7, L1, and/or L2, see page 4, lines 33-37. On page 5, lines 2-5, page, Stanley et al. teaches that component (ii) can comprise a recombinant vector encoding at least one papillomavirus protein or fusion protein, which teaches that the proteins are not limited to expression in fused form.

Although Stanley et al. teaches the use of a vaccinia virus vector in a papilloma vaccine, the reference does not teach which a particular strain of vaccinia. However, Boursnell et al. teaches expression of E6 and E7 from HPV16 and HPV18 in the Wyeth strain of the vaccinia vector for conditions caused by an HPV infection, see the abstract and page page 18, lines 1-4.

Administration of this composition had the lowest number of complications, see page 14, lines 17-25. Meyer et al. teaches six major deletion sites in the wild-type vaccinia Ankara strain during attenuation to MVA that are not essential to viral replication and attenuate virus pathogenicity, see the abstract, the results section on page 1032-1034. In addition, Meyer et al. teaches that the insertion of the K1L gene of the MVA vaccinia strain leads to increased host range and suggests this as a selection system for recombinant viruses expressing foreign genes, see page 1037, a third of the way down page 1037. Therefore, one of skill in the art at the time the invention was made would have been motivated to utilize the a vaccinia strain to express papillomavirus peptides, taught by Stanley et al., in a vaccine to treat the papillomavirus because of the large insertion areas provided by the non-essential viral genome that can be deleted without harming viral replication taught by Meyer et al. and to lower side effects that could be caused by administration of the vaccine, see Boursnell et al. on page 14, line 17 to page 15, line 12.

Further motivation to combine early and late polypeptides of the papillomavirus is found in the teachings of Galloway. Galloway teaches that prophylactic papillomavirus vaccine compositions encompass L1 and L2 and that therapeutic papillomavirus vaccines are based on E6 and E7, see the abstract. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the therapeutic effects of the early proteins and the prophylactic effects of the late proteins in order to treat patients, regardless of whether they were already infected or needed to prevent infection. One of skill in the art at the time of the invention would have had a reasonable expectation of success because of the prophylactic properties of L1 and L2 to confer immunity and the treatment of tumors demonstrated by E6 and

E7. Galloway teaches that L2 and E7 fusion proteins have reduced the number, severity, and duration of lesions, see the paragraph bridging pages 190-191. Galloway does not teach the use of IL-2 and B7.1 to aid in activating the immune response. However, Hines et al. uses IL-2 to stimulate the immune system as a whole, see the "cellular adoptive therapy" section on page 862-863 and figure 2 on page 863. It is well known in the art that IL-2 has a stimulating effect of activating cytotoxic T cells. Therefore, one skilled in the art would be motivated to incorporate IL-2 into a vaccine composition to further enhance the immune system response to the antigens administered in a vaccine. Hines et al. does not teach B7.1 or B7.2. However, Gajewski et al. teaches that B7.1 and B7.2 can also provide costimulator function for IL-2 production of CD4+ cells, see the introduction on page 465. Therefore, one skilled in the art at the time the invention was made would have been motivated to incorporate B7.1 and/or B7.2 in order to stimulate IL-2 production to activate cytotoxic T cells. Therefore, as evidenced by the references, the invention as a whole would have been prima facie obvious to one of skill in the art at the time of the invention.

In regard to the teachings of Galloway, Applicant argues that even though HPV proteins induce a humoral response, this does not correlate to a protective antitumoral effect. In addition, Applicant argues that Galloway et al. reviews responses in animal models to polypeptides, and makes no mention of vector-based compositions. Applicant argues furthermore, Galloway never discloses or suggests the use of both approaches, with the exception of L2 and E7 expressed as a fusion protein.

It is noted that Galloway did not disclose vector-based compositions, but other references did teach that limitation (see the teachings of Stanley et al., Boursnell et al., and Meyer et al. above).

Applicant argues references (WO 93/00436, WO 94/23037, WO 91/23037) on pages 24-25 that were not cited in the previous Office action. Therefore, the arguments concerning these references are unconvincing because they do not apply to the 103 rejection.

Applicant argues that the teachings of Hines et al. do not refer to a method of treatment involving administering an immunostimulatory molecule encoding sequence. Furthermore, Applicant argues that the teachings of Hines et al. is insufficient because the *ex vivo* approach to stimulating T cells is not used to specifically enhance anti-HPV immunity.

The teachings of Hines et al. were combined with the teachings of Stanley et al. Stanley et al. taught the use of an immunostimulatory sequence, IL-12 in a in a vector-based papillomavirus vaccine. Hines et al. teaches another immunostimulatory molecule, IL-2, to stimulate the immune system as a whole in an *ex vivo* approach to achieve anti-tumor responses to HPV infection, see "Cellular Adoptive Therapy" on pages 862-836 and figure 2. Therefore, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention in view of the teachings of Stanley et al., discussed above and the natural stimulating effect of IL-2 on cytotoxic T cells.

Applicant argues that Meyer et al. maps excision zones and that the instant invention incorporates polypeptides within deletions II and III. Applicant points out that the invention is not based on the site of integration of the polypeptides, but the combination of polypeptides within the vector.

Claim 38 specifically requires that the polypeptides be inserted in specific locations of MVA. Meyer et al. teaches that these zones are ideal for large insertions. Therefore, the teachings of Meyer et al. render this claim obvious to one of ordinary skill in the art, and as a whole render the invention as a whole prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al., Boursnell et al. (WO 92/16636), Galloway, Hines et al., Gajewski, and Meyer et al as applied to claims 32-49, 52-56 above, and further in view of Crook et al. and Munger et al.

The claims are drawn to an HPV-16 E6 protein modified by a deletion of amino acids 111-116 and an HPV-16 E7 protein modified by a deletion of amino acids 21-26.

See the teachings of Stanley et al., Galloway, Hines et al., Gajewski et al., and Meyer et al. above. The references do not expressly teach the claimed mutations.

Crook et al. teaches loss of the wild-type tumor suppressor function is achieved by the expression of HPV-16, see the last paragraph of column 1 on page 547. Crook et al. also teaches that an amino acid mutation in E6 reduces binding to p53 by 94% by deleting amino acids 111-115. Munger et al. teaches that E7 disrupts the retinoblastoma (RB) tumor suppressor gene by forming a complex with RB, see the abstract on page 4099. Munger et al. also teaches that the amino acid sequences necessary to form the complex formation with RB is located at a small stretch of amino acids surrounding the cysteine residue at sequence position 24, see the last 2 sentences of the introduction on page 4099. One of ordinary skill in the art at the time of the invention would have been motivated to utilize the specific deletions taught by the references to significantly decrease or eliminate tumor suppression in these proteins. The combined

references of Stanley et al., Galloway, Hines et al., Gajewski, and Meyer et al., Munger et al., and Crook et al. render the invention as a whole prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 7:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
May 18, 2001

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800
1600